ISSN 1936-8798/09/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2008.11.010

CLINICAL RESEARCH

Comparison of Drug-Eluting and Bare-Metal Stents for Stable Coronary Artery Disease

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Objectives The current study was designed to determine whether drug-eluting stents (DES) are superior to bare-metal stents (BMS) in patients with stable angina.

Background Percutaneous coronary intervention has been shown to decrease symptoms of angina; its use for stable angina has not been shown to reduce myocardial infarction or mortality.

Methods We conducted a retrospective, cross-sectional analysis of prospective data comparing the use of BMS versus DES in patients who met criteria used by the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) study investigators. The primary outcome was a composite of death, myocardial infarction, stroke, and revascularization on follow-up.

Results The 1-year primary event rate was 15% in the DES group (95% confidence interval [CI]: 11% to 18%), compared with 27% in the BMS group (95% CI: 23% to 31%, $p < 0.001$). A Cox proportional hazard regression model was used to adjust for differences in patient characteristics and showed a 1-year DES hazard ratio of 0.51 (95% CI: 0.36 to 0.71, $p < 0.001$). After 1 year, event rates for the primary outcome increased in DES subjects relative to BMS patients, such that longer follow-up analyses resulted in nonsignificant comparisons.

Conclusions These results suggest that the use of DES for patients with stable coronary disease is superior to BMS for 1 year, but that the increment in benefit decreased over continued follow-up. Further research is necessary to identify additional factors to promote longer-term efficacy and safety of DES. (J Am Coll Cardiol Intv 2009;2:321–8) © 2009 by the American College of Cardiology Foundation

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Manuscript received October 13, 2008; revised manuscript received November 10, 2008, accepted November 17, 2008.

Coronary heart disease is the leading cause of death in American men and women, accounting for 1 in 5 deaths in 2004 (1). Use of percutaneous coronary intervention (PCI) in the management of acute coronary syndromes has been shown to decrease mortality and myocardial infarction (MI) (2–4). The use of PCI as part of standard management for stable coronary disease remains controversial, however. Lifestyle modification, including dietary changes, exercise, and smoking cessation along with proper control of blood pressure, lipid profile, and diabetes is the guideline-based, first-line therapy for chronic stable angina (2,5). The use of PCI compared with medical therapy for stable coronary disease has been shown to decrease angina and improve short-term exercise capacity (6–8) but has not been shown to reduce mortality and risk of MI in prospective randomized trials (6–11). A number of limitations to these trials exist, such as the enrollment of a relatively low-risk patient population. In the initial studies, PCI consisted largely of angioplasty. A meta-analysis comparing angioplasty versus bare-metal stents (BMS) found no differences in death or MI (12). Similarly, several pooled analyses comparing the use of drug-eluting stents (DES) versus BMS for coronary artery disease have shown no difference with respect to death and MI (13–16).

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CABG = coronary artery bypass grafting
CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
IQR = interquartile range
MI = myocardial infarction
PCI = percutaneous coronary intervention

In the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, the addition of PCI to medical therapy resulted in no overall reduction in death, MI, or major cardiovascular outcomes when compared with medical therapy alone (17). However, DES were used in only 3% of patients receiving PCI. The question remains whether the use of DES may be beneficial. The current study was designed to address the hypothesis that, in a population similar to that studied in the COURAGE trial, the use of DES reduces the composite outcome of death, nonfatal MI, revascularization, and stroke compared with BMS.

Methods

Study design. We utilized a retrospective cross-sectional analysis of prospective data from the Mayo Clinic Rochester Coronary Catheterization Lab Registry, which includes follow-up data on death, MI, hospitalizations, cardiac events, and medication usage.

Study population. Subject inclusion and exclusion criteria mirrored the protocol used by the COURAGE trial. Specifically, we started with all patients receiving BMS from January 1, 1999, through March 31, 2003, and patients receiving DES from April 1, 2003, through March 31, 2007, who had consented to allow use of their records for research. Patients presenting with Canadian Cardiovascular Society class III or less angina were included. Patients were excluded if they presented with unstable angina, MI (within 7 days prior), cardiogenic shock or congestive heart failure, if they had ≥50% stenosis of the left main artery with no prior bypass, low ejection fraction (<30% or <35% if triple-vessel disease), PCI or coronary artery bypass grafting (CABG) within the last 6 months, a history of cardiac transplant, or cardiac arrest with ongoing cardiopulmonary resuscitation. In total, 874 stents were placed in 872 unique patients (Fig. 1). Within the BMS and DES groups, only the first qualifying PCI per patient was used for analysis.

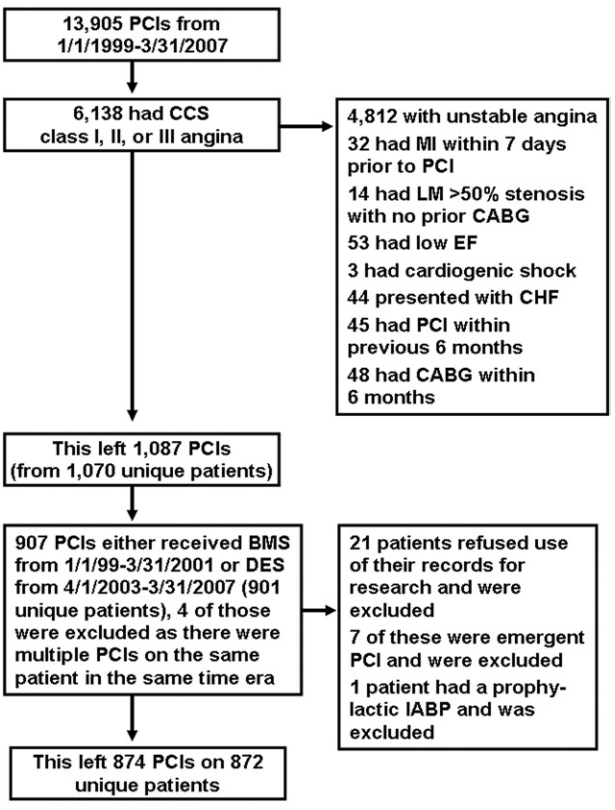

Figure 1. Selection Process

Flow chart depicting selection process of individuals studied. BMS = bare-metal stent(s); CABG = coronary artery bypass grafting; CHF = congestive heart failure; DES = drug-eluting stent(s); EF = ejection fraction; IABP = intra-aortic balloon pump; LM = left main artery; MI = myocardial infarction; PCI = percutaneous coronary intervention; CCS = Canadian Cardiovascular Society.

Treatment. In addition to the intervention, all patients undergoing PCI were seen in the Cardiovascular Health Clinic as part of their medical management. Data on medical management is recorded in Table 1.

Clinical outcome. The primary outcome measure was the composite rate of death, nonfatal MI, revascularization, and

Table 1. Clinical Characteristics

Variable	No DES (n = 474)	DES Use (n = 400)	p Value
Age, yrs	66.7 ± 10.5	66.0 ± 10.5	0.34
Male gender, n (%)	346 (72%)	291 (72%)	0.91
Canadian Cardiovascular Society class, n (%)			<0.001
I	10 (2%)	11 (3%)	
II	253 (53%)	290 (72%)	
III	215 (45%)	103 (25%)	
History of CHF, n (%)	17 (4%)	14 (4%)	0.91
Diabetes, n (%)	116 (24%)	128 (32%)	0.015
Hypertension, n (%)	358 (77%)	311 (80%)	0.28
Body mass index, kg/m^2	29.4 ± 5.5	29.6 ± 5.4	0.58
History of cholesterol ≥240, n (%)	385 (85%)	332 (86%)	0.74
Smoking status, n (%)			0.11
Never	188 (40%)	180 (46%)	
Former	235 (50%)	168 (43%)	
Current	49 (10%)	41 (11%)	
History of MI (>7 days), n (%)	139 (30%)	86 (22%)	0.009
Prior PCI, n (%)	121 (25%)	140 (35%)	0.002
Prior CABG, n (%)	106 (22%)	94 (23%)	0.67
Peripheral vascular disease, n (%)	47 (10%)	36 (9%)	0.62
CVA/TIA, n (%)	51 (11%)	33 (8%)	0.19
Moderate/severe renal disease, n (%)	4 (1%)	3 (1%)	0.88

Plus or minus values are mean ± SD, except those from the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) study data, which are median ± SD.

CABG = coronary artery bypass grafting; CHF = congestive heart failure; CVA = cerebrovascular accident; DES = drug-eluting stent(s); MI = myocardial infarction; PCI = percutaneous intervention; TIA = transient ischemic attack.

stroke during follow-up after PCI. Secondary outcomes included the individual outcomes from the primary end point, composites of death and MI, death and stroke, death and cardiac hospitalization, as well as severe angina. Successful PCI was defined as post-procedural stenosis ≤20% in at least 1 treated lesion and no in-hospital death, Q-wave MI, or CABG. MI was defined as the presence of 2 of the following: prolonged chest pain (>20 min), enzyme elevation ≥2× normal limit, ST-segment T-wave changes or new Q waves on serial electrocardiograms indicative of myocardial damage. Severe angina was defined as Canadian Cardiovascular Society class III or greater. Cardiac hospitalization was defined as meeting 1 of the following: hospitalization for unstable angina, MI, angiogram, CABG, any PCI (balloon, atherectomy, laser, stent, and thrombectomy), congestive heart failure, arrhythmia, heart transplant, or other cardiac surgery.

Follow-up. Database information regarding medication usage, symptoms, and hospitalizations was obtained via telephone. Patients were contacted at 6 month intervals for 12 months and yearly thereafter. This information, as well as records from other hospitals, was reviewed and entered in the database.

Statistical analysis. Continuous data are summarized as mean ± SD, except where noted. Discrete data are presented as frequency (group percentage). Differences between groups were compared using Student *t* test, Pearson's chi-square test, and the Mann-Whitney rank sum test for continuous, nominal, and ordinal data, respectively. Kaplan-Meier estimates were used to describe survival rates on follow-up after PCI, with the log-rank test employed to test group differences. Cox proportional hazards models were used to estimate adjusted hazards ratios for the DES effect adjusted for risk factors that differed significantly between the 2 groups. Schoenfeld residual plots were inspected to assess the plausibility of the proportional hazards assumption. When the assumption appeared to be violated, a likelihood ratio test comparing models with and without separate effects was conducted to determine the significance of the violation. The choice of follow-up time at which to model the divergence of effects was determined by visual inspection of the Schoenfeld plot for a range of potential cutpoints, followed by estimating the likelihood functions for models of various cutpoints.

Results

Baseline patient characteristics. We studied a total of 474 patients treated with BMS from the period of January 1, 1999, through March 31, 2003, and 400 patients receiving

Table 2. Angiographic Characteristics

Variable	No DES (n = 474)	DES Use (n=400)	p Value
Multivessel disease (70/50),* n (%)	336 (74%)	233 (65%)	0.010
Worst lesion type, n (%)			0.035
A	14 (3%)	7 (2%)	
B1	99 (21%)	78 (20%)	
B2	176 (38%)	127 (32%)	
C	177 (38%)	180 (46%)	
Maximum device size (mm)	3.4 ± 0.6	3.2 ± 0.4	<0.001
Maximum balloon length (mm)	16.9 ± 5.2	14.8 ± 4.0	<0.001
Urgency of PCI, n (%)			<0.001
Elective	309 (65%)	333 (83%)	
Urgent	165 (35%)	67 (17%)	
Number of segments treated	1.6 ± 0.8	1.6 ± 0.8	0.38
Total vessels treated, n (%)			0.69
1	381 (80%)	325 (81%)	
2	78 (16%)	67 (17%)	
3	15 (3%)	8 (2%)	
Vein graft intervention, n (%)	39 (8%)	11 (3%)	<0.001
Success rate,† n (%)	467 (99%)	397 (99%)	0.31

*Defined as 2 lesions greater than 70% and 50%; †defined as ≤20% post-procedure stenosis and no in-hospital myocardial infarction, death, Q-wave myocardial infarction, or coronary artery bypass grafting.
Abbreviations as in Table 1.

DES from April 1, 2003, through March 31, 2007. The baseline characteristics of both groups are found in Table 2, with angiographic comparisons in Table 3. Mean age was 66.6 ± 10.5 years for BMS recipients and 66.0 ± 10.5 years for DES patients. Seventy-two percent of both groups were male patients. Seventy-four percent of BMS patients and 65% of the DES patients had multivessel disease. Forty-five percent of BMS patients and 25% of the DES patients in our study had Canadian Cardiovascular Society class III angina. Overall, 65% of the BMS and 83% of the DES underwent entirely elective procedures. Eighty percent of the patients receiving BMS received 1 stent, and 81% of those with DES received 1 stent. Success rate, defined as post-procedural stenosis of less than or equal to 20% and no in-hospital death, Q-wave MI, or CABG, was 99% for both groups.

Medication and treatment targets. Follow-up medication data at 1 year was available in 81% of BMS and 84% of the DES group (Table 1). At year 1, angiotensin-converting enzyme inhibitors were used in 45% of the BMS group versus 56% in the DES group ($p = 0.001$). However, we did not have data on angiotensin receptor blockers, which may account for some of this difference. Another difference at year 1 was the use of lipid-lowering agents, as 83% of the BMS group versus 69% of DES patients ($p < 0.001$), were using these agents. Follow-up data on total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and body mass index was not available in our registry. Plavix (Bristol-Myers Squibb Co., New York, New York; and Sanofi-aventis, Bridgewater, New Jersey) use at year 1 in the BMS group was 10% and 38% for the DES group.

Table 3. Medication Use at Year 1

Variable	No DES (n = 474)	DES Use (n = 400)	p Value
Medication use evaluated at 1 year*	386 (81%)	335 (84%)	0.37
Aspirin use at 1 year	353 (91%)	317 (95%)	0.10
Beta-blocker use at 1 year	276 (72%)	255 (76%)	0.16
Calcium-channel blocker use at 1 year	96 (25%)	64 (19%)	0.06
ACE inhibitor use at 1 year	172 (45%)	189 (56%)	0.001
Lipid-lowering use at 1 year	320 (83%)	233 (70%)	<0.001
NTG use at 1 year	158 (41%)	120 (36%)	0.16
Plavix use at 1 year	40 (10%)	133 (40%)	<0.001

Values are n (%). *Data collected between 9 and 18 months after procedure.
ACE = angiotensin-converting enzyme; DES = drug-eluting stent(s); NTG = nitroglycerine.

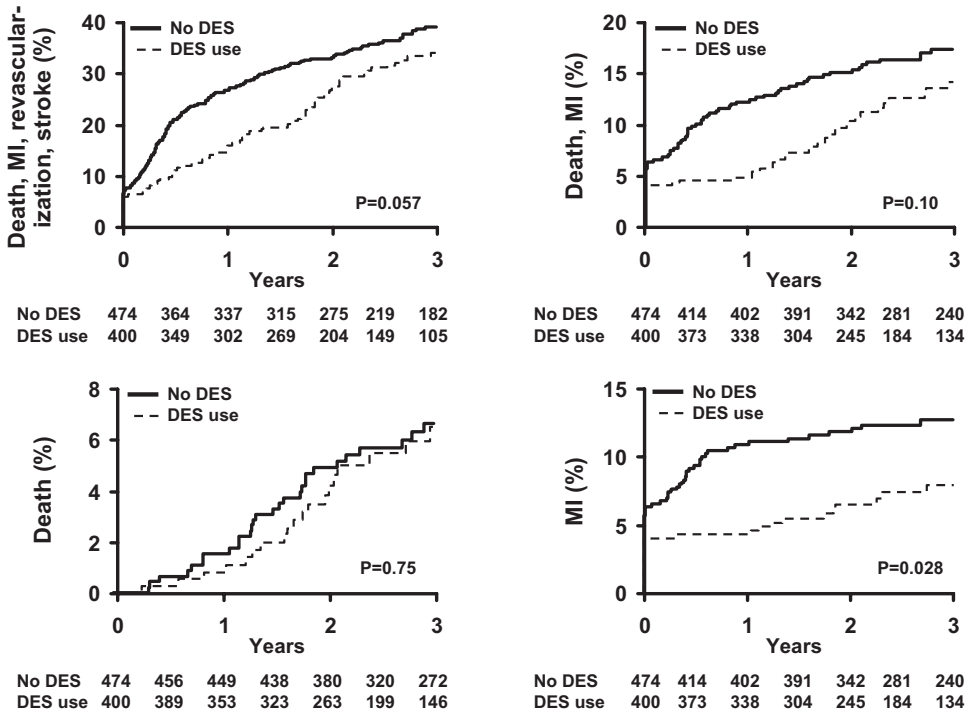

Figure 2. Kaplan-Meier Plots

Three-year outcomes of death/MI/revascularization/stroke, death/MI, death, and MI. Number at risk on x-axis. Abbreviations as in Figure 1.

Follow-up period. The median (interquartile range [IQR]) follow-up in the DES group was 33.7 months (IQR: 23.5 to 44.5) compared with 44.4 months (IQR: 28.8 to 57.3) in the BMS group ($p < 0.001$).

Primary outcomes. To adjust for differences in patient characteristics, a Cox proportional hazards regression model was used. Diagnostic plots indicated that the proportional hazards assumption (i.e., that the DES effect was constant over follow-up) did not fit the data for several end points, namely the composite of death, MI, stroke, and revascularization, as well as for MI, revascularization, severe angina, and the composite end point of death and MI. The diagnostics indicated a change in DES effect direction and magnitude around 9 months. The proportional hazards assumption appeared to hold for other end points. The models accounting for a different effect after 6, 7, 8, 9, 10, 11, and 12 months were computed to assess the best time at which to model the change in DES effect. For various end points, the highest model likelihoods were typically at 11 months, sometimes 10 months. In all cases, a cutpoint at 12 months yielded a better fitting model than a cutpoint at 9 months, so we rounded up from 11 to 12 months for the choice of cutoff.

The primary outcome, a composite of death, nonfatal MI, revascularization, and stroke, had a 3-year event rate of 34% in the DES group (95% confidence interval [CI]: 28% to 39%) compared with 39% in the BMS group (95% CI: 34% to 44%, $p = 0.057$) (Fig. 2). Based on the multivariable model, patients treated with DES were at significantly lower risk of events than BMS patients during the first 12 months after PCI (hazard ratio [HR]: 0.51, 95% CI: 0.36 to 0.71, $p < 0.001$) (Table 4). After 12 months, there was a trend toward increased event rates among DES patients compared with BMS patients (HR: 1.36, 95% CI: 0.94 to 1.96, $p = 0.10$).

Secondary outcomes. The 3-year event rate for the individual outcome of death showed no statistical difference between DES 7% (95% CI: 4% to 9%) and BMS 7% (95% CI: 4% to 9%, $p = 0.75$) (Fig. 2). The 3-year event rate of MI was significantly lower in the DES group, 8% (95% CI: 5% to 11%) versus the BMS group, 13% (95% CI: 9% to 16%, $p = 0.028$). The Cox proportional hazards regression model showed that at 12 months, DES patients were at significantly lower risk for MI (HR: 0.43, 95% CI: 0.24 to 0.78, $p = 0.005$). After 1 year, DES patients were at higher risk for MI (HR: 2.39, 95% CI: 0.99 to 5.78, $p = 0.053$) (Table 4). The secondary composite end point of death and MI had a trend toward benefit with DES; the 3-year event DES rate was 14% (95% CI: 10% to 18%) versus BMS 17% (95% CI: 14% to 21%, $p = 0.10$) (Fig. 2). The Cox proportional hazards regression model showed that patients treated with DES were at significantly lower risk for the composite of

Table 4. Outcomes

End Point	Kaplan-Meier Event % (95% CI) DES	BMS	Log-Rank p Value	Adjusted HR (95% CI); p Value*
Death/MI/revascularization/CVA			0.057	
12 months	15 (11–8)	27 (23–31)		0.51 (0.36–0.71); <0.001
3 yrs	34 (28–39)	39 (34–44)		1.36 (0.94–1.96); 0.10
Death			0.75	0.94 (0.51–1.73); 0.84
12 months	0.8 (0.0–1.7)	1.5 (0.4–2.6)		
3 yrs	7 (4–9)	7 (4–9)		
MI			0.028	
12 months	4 (2–6)	11 (8–14)		0.43 (0.24–0.78); 0.005
3 yrs	8 (5–11)	13 (9–16)		2.39 (0.99–5.78); 0.053
Revascularization			0.26	
12 months	11 (8–14)	20 (16–23)		0.50 (0.34–0.74); <0.001
3 yrs	26 (21–30)	28 (24–32)		1.60 (1.03–2.50); 0.039
CVA			0.14	0.85 (0.21–3.53); 0.82
12 months	0.3 (0.0–0.8)	1.1 (0.1–2.0)		
3 yrs	0.8 (0.0–1.9)	2.1 (0.7–3.5)		
Death/MI			0.10	
12 months	5 (3–7)	12 (9–15)		0.42 (0.25–0.73); 0.002
3 yrs	14 (10–18)	17 (14–21)		1.63 (0.96–2.78); 0.072
Death/CVA			0.38	0.95 (0.54–1.66); 0.85
12 months	1.0 (0.0–2.0)	2.6 (1.1–4.1)		
3 yrs	7 (4–10)	8 (6–11)		
Death/cardiac hospitalization			0.72	0.95 (0.73–1.24); 0.72
12 months	13 (10–17)	17 (13–20)		
3 yrs	33 (28–39)	34 (29–38)		
Severe angina			0.067	
12 months	11 (8–14)	19 (16–23)		0.61 (0.41–0.89); 0.011
3 yrs	24 (19–30)	30 (25–34)		1.16 (0.77–1.76); 0.48

*Where 2 hazard ratios (HRs) are presented, the first is the effect for the first 12 months, the second is the effect after the first 12 months. If there was no differential effect before and after 12 months, then only 1 HR is given to summarize the overall follow-up effect.

BMS = bare metal stent(s); CI = confidence interval; other abbreviations as in Table 1.

death and MI during the first 12 months after PCI (HR: 0.42, 95% CI: 0.25 to 0.73, p = 0.002). After 12 months, there was a nonsignificant trend toward increased events in the DES group (HR: 1.63, 95% CI: 0.96 to 2.78, p = 0.072). Revascularization, after correction with the Cox proportional hazards regression model, showed an advantage at 1 year for DES use (HR: 0.50, 95% CI: 0.34 to 0.74, p < 0.001) but increased risk at 3 years (HR: 1.60, 95% CI: 1.03 to 2.50, p = 0.039). Severe angina showed a trend toward benefit with DES at 3 years and after correction with the Cox proportional hazards regression model; this benefit persisted for 1 year (HR: 0.61, 95% CI: 0.41 to 0.89, p = 0.011) but showed a nonsignificant association afterward (HR: 1.16, 95% CI: 0.77 to 1.76, p = 0.41). The other individual secondary outcomes of stroke, composites of death and stroke, as well as death and cardiac hospitalization showed no significant differences (Table 4).

Discussion

This study compared the use of DES and BMS for the treatment of stable angina, as defined by the COURAGE trial entry criteria. After correcting for differences in patient characteristics, our primary end point, the composite of death, MI, cerebrovascular accident, and revascularization, showed a statistically significant reduction in events with use of DES compared with BMS at 1 year. The secondary end point of MI also had a statistically significant reduction in events with DES during this time period. Both effects persisted for 1 year, after which such patients were found to be at higher risk. These results were driven mostly by lower MI rates in the first 12 months after PCI. Adjusted HRs for the end points of death/MI, revascularization, and severe angina also showed statistically significant decreased risk 1 year after DES followed by increased risk at 3 years. The

remaining secondary end points of death, stroke, and the composites of death and stroke, and death and cardiac hospitalization had associations that did not reach statistical significance.

The primary end point, depicted in Figure 2, showed an advantage for DES, particularly during the early portion of the follow-up period. The Cox proportional hazard regression model showed that this benefit existed for 12 months. This may be explained by differences in medical therapy. First, this finding may be a result of cessation of dual antiplatelet therapy in the DES group. The registry data showed that there was no difference in the use of aspirin at year 1 in both groups. At year 1, however, the use of clopidogrel in the DES group was only 38%. Given the risk for late stent thrombosis, current guidelines recommend treatment with clopidogrel after placement of DES for 1 year (18). A recent study supports the concept of a clopidogrel rebound effect, as both groups of patients in this study—whether being treated with clopidogrel plus optimal medical therapy or clopidogrel plus PCI after acute coronary syndrome — had increased 90-day mortality after stopping the clopidogrel (19). In addition, in the current study, there was a significant difference in the use of statins at year 1, with 83% of the BMS and only 69% of the DES group on statins at this time. Collection of data regarding medication use was obtained via telephone at 9, 12, or 18 months and is subject to some degree of error; there is unlikely to be such a large difference in medication compliance in these groups. This discrepancy may also account for some of the loss of clinical significance near year 1.

The secondary end point of death showed no statistical difference between DES and BMS, but the adjusted composite end point of death and MI showed a significant benefit with DES at 1 year. The COURAGE trial, as well as a meta-analysis of over 18,000 patients by Stettler et al. (20), did not show any statistically significant benefit in reducing the composite of death and MI with use of PCI (17). The study of Stettler et al. (20), however, did show a trend toward lower death rates in sirolimus-eluting stents. In addition, Shishehbor et al. (21) showed that overall mortality was reduced in patients receiving DES versus BMS after 4 years of follow-up. Previous studies have showed reductions in death up to 3 years; Mauri et al. (22) showed that DES provided a reduction in mortality after 2 years, and Tu et al. (23) showed that DES reduced death up to 3 years.

In the current study, the composite of death and MI was largely driven by the reduction in MI during the first 12 months after DES and, like the primary end point, displayed a trend toward increased rates after 12 months. Discontinuation of clopidogrel may help explain this finding. A study of Swedish patients receiving BMS and DES—for any indication—reported a trend toward lower event rates for the composite of death and MI over the first 6 months after implantation of DES, with increasing rates afterward (14). The authors attributed this observation to an increase in late stent thrombosis and noted that most patients were taking clopidogrel for a maximum of 6 months. The finding of early reduction of death and MI in patients receiving DES followed by clopidogrel discontinuation and subsequent increased rates of events at 6 to 18 months has also been shown in an observational study (24). The current study's findings encourage further research to identify factors that may extend the protective period and mitigate risk.

A recent study comparing BMS and DES for off-label use showed decreased rates of repeat revascularization at 1 year for patients receiving DES (25). After adjusting for differences in patient characteristics risk factors, we also observed significantly less revascularizations in the DES group in the first 12 months after DES. However, there was a statistically significant increased risk of revascularization at 3 years.

Study limitations. This study is a nonrandomized, retrospective cross-sectional analysis of prospective data and has the inherent limitations of such a study. The 2 groups studied were from different time periods; thus, procedure date is confounded with treatment group. Selection of the 2 periods was used to increase sample size, as BMS-only cases matching inclusion criteria represented only 12% of DES cases during the DES era. This small sample size precluded a direct comparison between these groups during the DES era. In addition, we included 23 of 400 patients in the DES group who also had a BMS placed. This represents less than 6% of the DES group. We included a small percentage of patients whose procedure was classified as urgent, which may indicate a small increase in patient risk profile for a small subset of patients in this study. Follow-up at 1 year was completed in 96.2% of BMS and 89.5% of DES patients. One reason for this is that some patients may have been contacted slightly before 12 months; the 10 months follow-up rate is 93% in DES patients. The other reason is that, if after multiple attempts the patient was not reached by telephone, further attempts were deferred until the next scheduled call 12 months later. Medication use was evaluated at year 1 in 84% of the DES patients and 81% of the BMS group. The lower rate for medication follow-up may be due to patients discussing their hospitalizations and/or symptoms, but declining to take further time to additionally discuss medication use during follow-up phone calls. We were also limited in follow-up data regarding body mass index and cholesterol levels.

Conclusions

The current study demonstrated that DES for stable angina were shown to have a statistically significant reduction in the composite of death, MI, stroke, and revascularization com-

pared with BMS for the first year after stent placement. This was largely driven by decreased rates of MI and revascularization. However, at 3 years, event rates for the primary outcome increased for DES patients but resulted in a nonsignificant comparison, while the secondary outcome of revascularization showed statistically significant increase in events for DES subjects. These results suggest that the use of DES for patients with stable angina is superior to BMS for 1 year, but that the increment in benefit decreased over continued follow-up. Further research is necessary to identify additional factors to promote longer-term efficacy and safety of DES.

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Key Words: stable coronary disease ■ drug-eluting stent ■ bare-metal stent ■ myocardial infarction ■ mortality.